Reichert (Ed. T.) Compliments of the Author

*Extracted from the American Journal of the Medical Sciences for July, 1881.*



# ARE ALL ANÆSTHETICS DANGEROUS WHICH CONTAIN CHLORINE, BROMINE, OR IODINE?

BY

EDWARD T. REICHERT, M. D.,
OF NEWARK, NEW JERSEY,
*Formerly Demonstrator of Experimental Therapeutics and Instructor in Experimental Physiology in the Post-Graduate Course of Medicine in the University of Pennsylvania.*

[Extracted from the American Journal of the Medical Sciences for July, 1881.]

# ARE ALL ANÆSTHETICS DANGEROUS WHICH CONTAIN CHLORINE, BROMINE, OR IODINE?[1]

By EDWARD T. REICHERT, M.D.,

OF NEWARK, NEW JERSEY,

FORMERLY DEMONSTRATOR OF EXPERIMENTAL THERAPEUTICS AND INSTRUCTOR IN EXPERIMENTAL PHYSIOLOGY IN THE POST-GRADUATE COURSE OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA.

As early as 1849, Nunnelly (*Trans. Prov. Med. and Surg. Association*, xvi. 1849) stated that the effects produced by *chloroform* by a like quantity and in parallel circumstances, as far as could be ascertained, were similar but not identical, and that they were far more considerable in some cases than in others, and even upon the same animal the effects of the same dose were greater at one time than at another. Proof of this truth is not wanting, but is unfortunately only too plentiful, as is instanced in the frequent deaths which have been reported as occurring from the use of this agent, and by doses wholly out of proportion to the effects produced. To the experimental physiologist and therapeutist, similar cases occurring in animals during anæsthetization with chloroform must be numerous, if this agent has to any extent been employed; and, in speaking from personal experience in the chloroformization of some hundreds of animals, many such instances are recalled to mind,—some indeed, which are even the more striking because of sudden death occurring after the removal of the inhaler, and before complete anæsthesia was induced (see also Report Brit. Med. Assoc. Committee, *Brit. Med. Journ.*, 1879); and even deaths taking place in patients under similar circumstances are not want-

[1] It was the author's intention to give, in connection with the following notes, the results of a physiological research which has been commenced in this connection, but upon a second consideration it appeared doubtful as to how soon this investigation would be completed. As anything of practical value relating to anæsthetics must always be of momentary importance to the profession, and as there is much to be learned from the literature of the subject alone, and as there are many facts herein contained which are of considerable interest and not generally known, and may prove of immediate value to both the therapeutist and experimenter, it was deemed best not to withhold this portion of the paper, but rather to let the record of the experiments follow as a separate article.

ing, as is attested by Kappeler (*Part XX., German Surgery*, by Billroth and Luecke, quoted by Reeve), and by records of chloroform deaths already reported. In Kappeler's case death occurred in two minutes after the administration of chloroform had been stopped. In the report of the British Association's Committee on their experiments on animals it is stated that in two instances sudden and unlooked-for effects on the heart occurred after more than a minute had elapsed since the administration of any chloroform. My own experiments on animals with the *ethyl bromide* have yielded similar results, and so strikingly analogous that I can safely assert, that, were the results of my experience with the deaths following the use of chloroform and the ethyl bromide in anæsthetization tabulated in parallel columns, not even the keenest observer would be able to tell which was which. In the laboratory the bottles containing these compounds were on the table together, and were employed without any special choice, the nearest or handiest being used; and I must acknowledge that, where death ensued, as it did in quite a number of instances, the only way I knew which one of the two was the cause of it was by resorting to the odours of the two, and thus distinguishing them—their toxicological effects being so similar as to be beyond the power of discrimination. The same remarks apply equally well and with equal positiveness to several other chlorinated and brominated anæsthetics, and the list could be considerably amplified were it necessary, or did space permit.

That the halogens are decided and general depressants of the animal organism is a fact undisputed by the therapeutist; that they exert a special depressant influence on the heart is universally conceded; and that most of the compounds in which either of these elements enters, especially in an elementary form and in any well-marked or appreciable proportions, partake to a greater or less extent of this depressant quality, and more especially so, if the elements are in a loosely molecular condition, such as is probably the condition in all ethers, is also acknowledged. Consequently, in looking over the list of compounds used as anæsthetics (some thirty or forty in number), it was a noticeable fact that the compounds containing either of these elements were, as a rule, unmistakably more dangerous than others; and the obvious reason of this was the presence of one or the other of these principles, which, being in a probably loosely molecular combination, acted either in combination as such, or were readily dissociated under favourable conditions, and at such times made their decidedly paretic action on the heart manifest. The writer would not here be understood as inferring that either in these toxic elements, or in their probable liberation in the system alone, resides the power of causing sudden, abnormal, and overwhelming effects, or of being invariably the cause of sudden death; for it must be apparent that peculiar idiosyncrasies, general asthenic conditions and especially so of the heart, the greater impressionability of the heart or of its nervous mechanism at times than at others

(even in apparently normal states of the economy), variations in the temperature of the surrounding media causing a greater volatility of the compound used, and the necessarily greater concentration of the vapour inhaled, etc. etc., must play at times a very important part in such cases. However, that all chlorinated, brominated, and iodated anæsthetics may act at times altogether out of proportion to the dose and under similar circumstances, and that those which have already been used to any extent have done so, is well attested in the papers already written, or by experiments recently made by myself on animals, as well as by the numerous deaths which have been reported from the needless use of this group of substances.

To look over the death-list from anæsthetization by this particular class of compounds, and in cases in which they were not especially indicated, and where some of the safer anæsthetics, such as ether, would have answered the purposes required, and where they have been unjustifiably used before their physiological actions were previously determined by experimentation on animals, and their safety assured or their dangers indicated, is positively appalling; while the number of cases, almost innumerable, where life's fragile thread was almost broken, the trusting patient but snatched from the chasm of death by the timely administration of physiological antidotes or the almost superhuman efforts of the physician and attendants, is alike shocking. Let us but glance at the chloroform death-list, and, as horrible and incredible as it may seem, there have been *reported* an average of about *a death for every month since the time of its introduction.* With this array of fully authenticated cases before us, what, indeed, must be the actual number?—for it must be conceded that probably double, triple, or quadruple as many more were not reported, and will never come to light. Even Kappeler alone says that he knows of four cases never reported, and personally I know of two. However, it needs no words of mine to remind the profession of the dangers of chloroform; so let us but briefly notice several others of this class of anæsthetics.

*Methylene Bichloride*, which was introduced by Richardson (*Med. Times and Gaz.*, 1867, p. 478) as a pleasant anæsthetic, but in connection with which he expressed no definite opinion as to its safety, has now been entirely cast aside by the profession as being entirely too unsafe. Kappeler says that experience shows it to be as dangerous, if not more so, as chloroform, and furnishes a list of nine cases of death from its use. Unfortunately, I have not had a copy of Kappeler's work at my disposal; but in looking over the details of cases published in the journals to which I have had access (*Med. Times and Gaz.*, 1869, ii. p. 524; *Lancet*, 1869, p. 582; *British Medical Journal*, Sept. 1871; *Pharmaceutical Journal*, 1871, p. 875, two cases; *British Medical Journal*, August, 1872; *Lancet*, 1873, i. p. 23; *Ibid.*, 1877, ii. p. 26), I have found that in several of them doses of a drachm and a half caused death, and, judging from the symptoms, it must be undoubted that death ensued in some of them at least

from cardiac paralysis. The experiments made by the British Committee on frogs show that the heart becomes slowed and is soon stopped, and that *the heart was affected the same as by chloroform*, the first sign of paralysis being the distension of the right ventricle. Even were it not certified by the above Committee that it affects the heart like chloroform, the fact of death occurring after doses but ordinarily sufficient to produce anæsthesia is sufficient to impress every one with the truth that it acts, like chloroform and ethyl bromide, wholly out of proportion to the dose.

Let me revert to *ethyl bromide* or *hydrobromic ether*, which has but recently come into vogue through the recommendation of Turnbull and of Levis, and which has, during the few months of its usage, and indeed very limited usage, added proof to the above-asserted toxic properties of all the brominated anæsthetics. In referring to the articles published by these gentlemen, one is at once impressed with the strong recommendations given the ether, and the enthusiasm experienced in the discovery of so valuable a compound; and Levis (reprint from *Medical Record*) stated, that practically it was the best anæsthetic now in use. But, if what he previously asserted, that "the physiological action of the bromide of ethyl did not incline to the dangers of cerebral anæmia and cardiac syncope, which sometimes occur in chloroform, and that no tendencies in such a direction seemed to threaten," were proven true by subsequent investigation, the ether would not so early have fallen into disuse. And had experimental investigations been pursued in the lower animals previous to those on man, like those by Wood (*Phila. Med. Times*, 1880, p. 370), such unfortunate results would probably not have followed in Levis's, as well as in the hands of others who have followed in his footsteps. While advising his practitioners to be cautious in its use, Levis describes the method of administration preferred by himself, which, in our opinion, is of itself dangerous. His method is this, that "in commencing the inhalation of bromide of ethyl to make a rapid and decided impression, with the lint and napkin held closely over the nose and mouth of the patient." If we have here an agent proven to be dangerous, if not quite as dangerous as chloroform, it needs no further argument to show that the same precautions must necessarily be observed in its administration as with its more popular predecessor.

Squibb (*Medical Record*, 1880, p. 379) warns those who use bromide of ethyl to be cautious, because he deems it of the nature of a loosely molecular compound, and hence he argues its liability to become broken up in the system and bromine liberated. Although the experiments of Wolff (*American Journal of Pharmacy*, 1880) would seem to show that this change does not occur out of the body, yet as we do not know in what form the ether is eliminated, and that fatal effects have followed its use, which resembled those in bromine-poisoning, we are bound to accept Squibb's assertion with deference, at least until it is proven to be otherwise than correct.

But whether bromine is liberated or not does not affect the argument, for we do know that Wolff (*loc. cit.*) found that death occurred in one of his experiments on rabbits, and that it typically resembled that caused by chloroform by sudden cardiac failure; and Wood (*loc. cit.*) has proved that it is a direct cardiac depressant, which I have fully corroborated by my own experiments, and have further indisputably proven that it at times acts altogether out of proportion to the dose used, as already stated; and that at least two deaths have followed its use (Sims, *Medical Record*, 1880, p. 361; Levis, *Medical News and Abstract*, June, 1880). Moreover, several cases have occurred in Philadelphia hospitals in which such alarming symptoms occurred that only by the most strenuous efforts could the patients be rescued from impending death; and a case of this nature is reported by Little (*Medical Record*, April 3, 1880); and other instances, where the administration was stopped, or the ether was refused to be given by resident physicians through absolute fear of disaster, could also be given.

It will, however, undoubtedly be said, and indeed has been said, that neither of the cases reported by Sims or Levis was due to the use of anæsthetics *per se:* in the former instance because of the very depressed condition of the patient; and in the latter because death did not occur until many hours following the administration of the anæsthetic. But in connection with these cases we know, first, that Emmet (*Gynæcology*, 2d edition, p. 746) called the attention of the profession to the danger of administering anæsthetics where any disease of the kidneys exists because of the active part taken by these organs in the elimination of them; second, that Squibb asserts that bromide of ethyl is a loosely molecular article, prone to undergo decomposition in the system and to liberate free bromine; 3d, that ethyl bromide is a marked cardiac depressant, as proven by both Wood and myself, by actual examination. Sims's case certainly did have symptoms in harmony with those caused by some toxic agent such as bromine. The woman also had a marked scantiness in the secretion of the urine, and on post-mortem examination it was found that she had acute catarrhal nephritis, indicating that the kidneys were disabled from performing their function in eliminating the ether, hence its retention and its probable decomposition in the economy, with the subsequent toxic symptoms. In Levis's case it seems plain that a simple explanation of the death of the patient lies in the fact that the heart, which had become so enfeebled from exhausting chronic disease, was unable to bear the strain of the powerful depression of its already diminished powers that ensued upon the administration of the anæsthetic, and as a consequence broke down under the excessive load.[1] And lastly, as evidence going

[1] An analogous instance of a medicine apparently acting out of proportion to the dose is illustrated in the incipient stage of typhoid fever, where, on account of an irritative condition of the bowels, an ordinary cathartic dose will produce hypercatharsis.

towards proving that Sims's case was due to bromine-poisoning, and in corroboration of Squibb's assertion, I quote from experiments made by Nunnelly (*loc. cit.*, 327) with a similar compound, the *Ethylene Bibromide*, as well as with the *Ethyl Iodide* (*loc. cit.*, p. 324), in which similar results followed, in so far that the animals appeared perfectly well after the experiments, but all of them, after some hours, perished from *blood-poisoning* (see, also, *Ethyl Iodide*, *Methyl Iodide*, *Iodoform*).

*Methyl Iodide*, which was introduced some years ago, has never come into general use because of its being considered unsafe by both Richardson and Simpson. The former observer (*Med. Times and Gazette*, ii. 1870, p. 470) found it to cause great excitement of the heart and circulation, which was evidently a sign of cardiac depression, if what he thought was true, that the *iodine* was the efficient cause of the phenomena which lie outside of the narcotism. He further certifies that the *Amyl Iodide and Chloride act similarly to the Methyl compound.*

*Chloral Hydrate*, although not an anæsthetic in a therapeutic sense, has, like chloroform, and ethyl bromide, given us painful instances of its acting at times altogether out of proportion to the dose. Fuller (*Lancet*, March, 1871) quotes a case where thirty grains caused death in a young lady. Schwaighofer (*Irish Hospital Gaz.*, 1873) reports another of a drunkard, in which a drachm produced death; and three other cases (Reynolds, *Practitioner*, March, 1870; Watam, *Med. and Surgical Reporter*, Jan. 1871; Fuller, *loc. cit.*), in which forty-five, eighty, and thirty grains respectively caused alarming symptoms, and from the large dose death nearly ensued. Death has resulted from a dose of ten grains (*American Dispensatory*, 1880, p. 396). Other deaths have been reported (*Medical Times and Gaz.*, 1871, pp. 131, 672; Norris, *Lancet*, 1871, i. p. 226, and Browne, *ibid.* p. 574), and in some of these cases indisputable evidences of its power of weakening the heart were present. Did chloral hydrate become decomposed in the system into formic acid and chloroform (Personne, *Journ. de Pharm. et Chimie*, 1870; and Pellogio, *Schmidt's Jahrbücher*, bd. cli. p. 89; Liebreich *Wiener Med. Wochensch.*, Aug. 1860), we could readily account for its acting at times in a manner wholly disproportionate to the dose, and for its being a cardiac depressant; but as recent investigations disprove this theory (Hammertin, *Schmidt's Jahrbücher*, bd. cli.; Rajursky, *Ibid.*, bd. cli.; Amory, *N. Y. Med. Journ.*, 1870; Djurburg, *Schmidt's Jahr.*, bd. cli.; Leurison, *Archiv Anat. u. Phys.*, 1870), we must look elsewhere for this toxic principle.

*Hydriodic Ether* or *Ethyl Iodide*, also used by Nunnelly (*loc. cit.*, p. 324), was found to be so dangerous as to entirely preclude its use in medicine for anæsthetic purposes; and he states that whatever anæsthetic property it might possess (and this is not insignificant) it never could be employed in practice, as its action is so very deleterious; for out of the four animals experimented upon, three of which were rendered insensible,

all died, and the fourth had not sufficient of the vapour to render it in the least insensible, and yet for two or three days it was doubtful whether it would recover. Like the bromide of olefiant gas (ethylene bromide), its immediate effects were not so dangerous as the consequences of inhalation were in a few hours; even when not enough to produce insensibility had been used, and when the animal to all appearances had been perfectly well, death would supervene. In one case the odour of the ether was distinctly perceptible in the brain twelve hours after death, and Nunnelly thinks that death was caused by *blood-poisoning*. Therapeutically it has been used in recent years "*by inhalation to bring the system speedily under the influence of iodine.*" (*National Dispensatory*, 1880, p. 114.)

*Bromide of Olefiant Gas* or *Ethylene Bromide* was also condemned by Nunnelly (*loc. cit.*, p. 327), who stated that, although it produced insensibility, it caused the respiration to become laborious, and although the appearances of distress speedily disappeared when the animals were released, yet in a few hours they all, without exception, died. He further remarks that in this respect it differs from other (?) anæsthetics, because of the animals appearing well immediately following the experiments, but soon dying. He attributes this effect to *blood-poisoning*.

*Iodoform* was not sufficiently volatile to cause anæsthesia (Nunnelly), but, from what we know of its use, when given per stomach or used locally, it possesses powerful anæsthetic (analgesic) properties. Unfortunately it has not been used sufficiently internally, nor have physiological experiments been pursued to such an extent as to give us an accurate knowledge of its action on the economy; yet we do know that it diminishes the pulse-rate, produces muscular and nervous debility, and is decomposed in the body, and that, when applied to mucous, serous, or abraded surfaces, it *becomes decomposed by the fat, and the iodine is eliminated from the body in the form of soluble iodides*. If iodine is liberated in the system, no further comment is needed.

*Carbon Dichloride* or *Chloric Ether* has been used to a sufficient extent to indicate that it produces distinct cardiac depression.

*Bromoform*, which possesses undoubted anæsthetic properties, was found in experiments of my own to powerfully depress the heart, and in one experiment on a small dog the intravenous injection of thirty minims of the preparation caused immediate cardiac arrest. Consequently, it was considered useless to pursue any further investigation in this line.

*Tetrachloride of Carbon* ($CCl_4$) was used by Laffont (*American Dispensatory*, 1880, p. 354), who found that it caused great debility of the heart, and lowering of the vascular tension. Simpson (*Medical Gazette*, 1865, ii. p. 651) previously used it under the name of *Bichloride of Carbon*, or *Chlorocarbon*, and more recently the same compound has been used by Smith (*Lancet*, 1867, i. pp. 575, 660). The latter observer found, in the post-mortem examinations of the animals experimented on, that

the auricles were much distended with blood, and especially on the right side. He noticed that the heart did not beat after the cessation of respiration, and that the pulse was decidedly lowered. In conclusion, it is stated that "when pushed to extremes it seems to destroy life by causing an arrest of the circulation of the blood through the lungs, a distended condition of the right side of the heart, an insufficient supply of blood to the left side of the heart, and consequently diminished systemic circulation."

*Chloride of Ethydene*, or *Ethylidene or Ethidene*, was first used by Snow (*Anæsthetics*), and more recently by Liebreich (*Med. Times and Gazette*, 1870, i. p. 642); the British Medical Association Committee (Action of Anæsthetics, *British Medical Journal*, 1879); Bird (*Medical Times and Gazette*, 1879, i. pp. 62); and Reeve (*New Remedies*, Nov. 1880, p. 334—quoted from *Chicago Med. and Surg. Examiner*, June, 1880). Liebreich considers it somewhat safer than chloroform; the British Committee found an enormous diminution in the arterial pressure, and that the heart-beats became so infrequent as to be virtually ineffectual in supplying the respiratory centres with blood. Bird esteems it a powerful cardiac stimulant, and states that all the patients under its influence presented the appearance of a strong cardiac stimulant, but that he would not like to keep a patient long under its influence for fear of a reaction in the opposite direction. His investigations were not carried far enough to justify this conclusion of its cardiac action, and, as his conjecture is contrary to the results of all other investigators, it must be rejected as untenable. Reeve found a diminution of blood pressure, which differed from that caused by chloroform, because it did not advance to complete extinction, nor exhibit such wide variations in its effects at different times in the same animal. A death from its use in Berlin has been reported by Kappeler (*loc. cit.*). Steffer (Binz's *Evidences of Therapeutics*, p. 69) says that it resembles chloroform in ultimate action, yet is not so dangerous.

*Ethylene* or *Ethene Bichloride*, or *Dutch Liquid*, was used by Nunnelly (*loc. cit.*), who speaks of it in a decidedly laudable way, stating that just as small a quantity will produce anæsthesia as chloroform, but that a much larger quantity is required to destroy life. Simpson (*Edinburgh Medical Journal*, 1848, vol. viii. p. 740) also made some investigations with it, and found that when its vapour was inhaled, it caused so much irritation in the throat that but few persons could endure inhaling it until anæsthesia was produced, and that the condition of anæsthesia was not attended with any excitement of the pulse. On himself it produced such a degree of irritation in the throat that it did not disappear for many hours. Recently, the British Committee (*loc. cit.*) used it, and report that no anæsthesia was produced up to the commencement of convulsions. The results of a series of experiments (*Phila. Med. Times*, May 7, 1881)

made by the writer with this compound indicate that it is a powerful anæsthetic, and that it fulfils considerable that Nunnelly claimed for it. It is undoubtedly a direct cardiac depressant. Why the British Committee got such anomalous results is rather curious.

*Butyl Chloride* (British Committee) caused the cardiac pulsation to become weaker, and finally extinguished; while *Methyl Chloride* only effected drowsiness. *Isobutyl Chloride* was not noticed as regarding any cardiac action.

Notwithstanding the fact that the above array affords indubitable proof to warrant the assertion that probably all chlorinated, brominated, or iodated anæsthetics do act as cardiac depressants, and goes to sustain Squibb's belief of their molecular condition, and as it likewise shows that unexceptionally, where used to any extent whatever, they have produced death by doses wholly disproportionate to ordinarily cause such a result, yet it is but a little venture to further assert that were any of these compounds, of which either of the above facts has not been proven to be true, to be investigated thoroughly by experimentation in the lower animals, doubt would no longer exist of the correctness of this belief.

A most interesting question here arises as to the *modus operandi* by which anæsthetics produce death, and one, indeed, which has constantly been in the minds of those particularly interested in these compounds, and consequently, as Reeve writes regarding chloroform, "we have had explanations without number, hypotheses the most untenable, and theories the most fantastical; ingenuity has been taxed to the utmost in the formation of some of them, and logic torn to tatters." Thus we have had theories depending upon mechanical, chemical, and physiological effects; stoppages of the air-passages with mucus, or by the falling back of the tongue; impurity of the compound used; idiosyncrasies of the patient; abnormal condition of the system; degree of concentration of the vapour; emotion or peculiar mental condition of the patient, such as fear of the possible consequences of the inhalation; improper methods of administration; the greater impressionability of the heart at times than at others, etc. And, as to the cause of death, about as many theories and as diverse have been advanced. But, without entering into all this distressing detail, it is only necessary to state that it is conceded that whatever may be the conditions favouring death, it does occur practically from either asphyxia or syncope, and that the latter condition may be the result of either a direct action on the heart, or by the inhibition of the heart through a stimulation of the inhibitory apparatus. But doubt can no longer exist that death in man in a vast majority of cases is the result of a paralysis of the heart itself by a direct local action, and not of a reflex nature by acting on the inhibitory nerves. The former has been proven; the latter not. It is also equally certain, except in cases where the vapour has been administered for a prolonged period in very dilute form, that death very seldom is the

result of asphyxia, so that, practically, sudden deaths are due to cardiac paralysis.

Just why it is that the heart appears to be more impressionable at some times than at others, and why a person may be safely anæsthetized several times with chloroform, and on a subsequent occasion and under similar circumstances perish during its administration, is a question which has called forth many answers, some of which are as fanciful as the processes advanced to account for the deaths themselves. The whole answer *practically* can be simply and satisfactorily contained in the single word—*dosage*. It is one thing, as we all know, to give a man a grain of morphia in divided doses and spread out over several hours, and another to give him the whole at a single dose; and just as true is it, that it is one thing to give a drachm or two of chloroform in a few inhalations, or to give it slowly during a period of some minutes. And while it is one thing to give a medicine hypodermically or by the stomach, it is yet another (in effect) if given intravenously; and especially so, in regard to medicines affecting the heart or nervous centres; and any one who has watched the blood-pressure of animals under the influence of chloroform must have been struck with the remarkable variations and the diminution of heart-beats which occur after each fresh administration, and of the sudden deaths often occurring immediately after, while, if the drug has been given by the stomach or hypodermically, these remarkable phenomena are comparatively absent. The drug when given by inhalation is absorbed so rapidly that practically it acts as an intravenous injection, and reaches the heart in a state of concentration almost as great; where, on the other hand, it must be slowly absorbed from the stomach or subcutaneous tissue, the drug reaches the heart in such a dilute condition as to be unable to make such a decided impression, and as a consequence when death ensues it is from asphyxia, the same as when the vapour of chloroform is given very dilute and for a prolonged period. Reeve (*Am. Jour. of Med. Sci.*, p. 199, July, 1880) says, that "we find no such idiosyncrasies in regard to other medicines," and that "opium, strychnia, and arsenic never cause death when administered in ordinary doses." Although this is not by any means a parallel case, because neither of these medicines is ever administered either by inhalation or by intravenous injection, nor are they decided cardiac depressants, yet deaths have occurred from the use of morphia in ordinary doses, when given hypodermically; for a death ensued in one case from an injection of one-sixth of a grain. Just now I recall a better instance, and in connection with apomorphia; a drug which promised to be the most valuable emetic of the Pharmacopœia, but which has been almost entirely abandoned for therapeutic purposes. This drug was asserted by some of the early investigators not to affect the heart or arterial pressure, but more recently the reverse has been found true (and conclusively proven by my own experimentation). In clinical medicine such alarming symptoms of a syncopal condition

and threatening collapse were induced by "*very small doses*" (ordinary doses), that it is never used in this country as an emetic except in cases of extreme emergency.

Doubtless, if time permitted such a laborious research in the literature before me, similar instances could be found where other cardiac depressants acted in this way,[1] and scarcely anything could be more safely predicted than that, if it were the custom and practicable to give this class of remedies by inhalation or by intravenous injection, deaths from them would be proportionately as great as from the popular anæsthetics under consideration; and there likewise can be no doubt that the reason they are looked upon as being safe is simply because they are never given by the above method, or in such doses as to produce such a profound impression on the system as is necessary to produce in anæsthetization; and hence they are absorbed relatively so slowly as to reach the heart in an exceedingly dilute condition, as already stated. An example illustrating the difference in the effects of intravenous and subcutaneous administration of the same amounts, I quote from my experiments with apomorphia (*Phil. Med. Times*, Dec. 1879) on animals in which the heart was sepa-

[1] Since the above was put in type, the writer is enabled to cite several instances in corroboration of this belief, and which are only the more valuable because of their illustrating the truth of it in three of our principal cardiac depressants. The first is a death which occurred in an adult in three hours from five grains of the fresh extract of *aconite* (Pareyra and Perrin, in *Buchner's Report für die Pharm.*, No. 68, p. 199, and *Med. Chir. Rev.*, Oct. 1839, p. 544; quoted by Tucker, *N. Y. Journ. of Med.*, 1854, i. p. 230). Two others took the same amount and received the same antidotal treatment and recovered. Tucker does not state what extract it was, whether of the root or leaves, but as it was probably the latter, and as the usual therapeutic dose is one or two grains, and twenty grains or more have been used during the day, it appears to be an interesting case for us. It will also be remembered that three drops of the saturated tincture of the root caused alarming symptoms (*National Dispensatory*, 1880, p. 97). This tincture (Flemings's) being two-thirds the strength of a fluid extract gives the amount of the drug in the dose taken as equivalent to one grain of the pure drug, or equal in a physiological point of view to from four to six grains of the leaves, or from a half to three-fourths of a grain of the extract of the leaves of the British Pharmacopœia. If the first case is not altogether a fair one as an illustration, because of the uncertainty of the preparation used, yet it will be admitted that the last one is. Headland (*Lancet*, July, 1856) gives an instance where fifteen drops of the tincture nearly proved fatal. A case is reported of a medical student (Andral's *Clinique Médicale*, Spillan, 1836, p. 698; quoted by Taylor, *Guy's Hospital Reports*, 1857, p. 415) who died in four hours from the effects of *two* grains of *tartar emetic*. Another is given by Richelot (*Ibid.*) of death in a child of four years from one-third of a grain. Moreover, Noble states (*Guy's Hosp. Rep.*, 1857, p. 415) that prostration and collapse followed in four cases of infants from ordinary doses. I have not yet seen his original paper. Stillé quotes a case of a woman in whom alarming symptoms were caused by half a grain. Nunnelly, from the results of a series of experiments on animals with *hydrocyanic acid* (*Med. Gaz.*, xl. 1837, p. 508), apprehends that the same creature is "liable to be seriously affected by a dose which at another time would produce but little effect." I will take occasion to resume a discussion of this subject at an early day.

rated from any central nervous influence, and so practically isolated, where after a subcutaneous injection no effect on the arterial tension was apparent, yet after an intravenous injection of the same amount, the arterial pressure was decidedly reduced, showing that although in both cases the dose was the same *apparently*, yet *practically* it was vastly different, and while it was evident that repeated subcutaneous injections could be borne with relative freedom from danger, on the other hand, regarding intravenous injections, it must be obvious that the reverse is true. That this argument is equally applicable to anæsthetics needs no further comment.

Moreover, there can be no doubt that the heart and other parts of the system, but especially the former, are more readily influenced at times by impressions, both intrinsic and extrinsic, than at others, and particularly so in those persons possessing a nervous temperament; and it is not an uncommon thing for such individuals to experience, on some occasions, a palpitation, or some vague or indefinable sensation about the heart, while at others, under similar circumstances, they would appreciate nothing of the sort. If, therefore, the heart and other vital parts are at times more susceptible, and more readily influenced by mental or other intrinsic impressions at certain but indefinite periods, why is it not probable that they are more susceptible at these periods to extrinsic influences, such as medicines? If this is so, and we probably have good illustrations of the truth of it in the instances already given, it is not difficult to conceive how the same dose, under apparently similar circumstances, may have double the effect it would have had on other occasions. As, for instance, let us illustrate the resistance of the heart to a given drug as being 10: if, now, the resistance is reduced to 5 by causes which we do not as yet understand, it is readily understood how the same dose will produce a given effect in the first instance, and double the effect in the second. If we now superadd to this changeableness of the impressionability of the heart a second factor, as shown in the very excessive variability of the degree of concentration of the vapour inhaled, the subject is made still more comprehensible, and it certainly requires no stretch of the imagination, when the many surrounding and modifying conditions are considered, to understand how it is that some inhalations may contain a very large percentage of the anæsthetic, and others relatively less, and, as a consequence, how a comparatively larger quantity may thus reach the heart at one time than at others. For it must be obvious, when we consider these conditions attending the administration of an anæsthetic, that the drug does not reach the heart in a steady supply, but gaining entrance into the pulmonary acini in an ever-varying degree of concentration, sometimes in large, and at others in small quantities, it must be certain that it reaches the blood in similarly varying proportions, because it finds its way into the circulation immediately, and, as a consequence, its action on the organism must then be analogous to repeated

intravenous injections of similarly varying amounts. For the sake of illustration, let us assume that when a given anæsthetic is administered the depressant effect on the heart is 10, and that now, as a result of the modifying conditions, the average degree of concentration of the vapour is doubled, is it not evident that the depressant action on the heart will be doubly felt? And now let us suppose we have a condition of the system when the heart's resistance is only half the normal, and we have the average degree of the concentration of the vapour considerably increased, it is readily conceivable as to how death may supervene.

To reiterate: it therefore must be apparent that we have here two important and self-evident factors, representing, respectively, two modes by which dosage is materially affected, and in accounting, in part at least, for the capriciousness in the action of chloroform and other cardiac depressants at different times under apparently similar circumstances, and a satisfactory explanation of the reason of their acting on such occasions altogether out of proportion to the dose used, and of the occurrence of death from ordinary anæsthetic doses.

Further, when we have a compound acting on the heart as a depressant, of a probable loosely molecular combination, which is liable to undergo under favourable conditions a decomposition in the blood, and of a composition which contains an element which, in a free state, is even more deleterious to the heart than the preparation itself, we certainly have added still another dangerous property.

It seems opportune in this connection to say a word in reference to the action on the nervous system, for we also have instances of the capriciousness of the action of anæsthetics, and of deaths as a result of *shock*, which are attributed to a sudden overwhelming of the nervous centres, and are, therefore, but other instances illustrating what was stated with particular reference to the heart in a previous paragraph. But the nervous system appears to be more strongly fortified against these sudden paretic impressions than the heart, and, as a consequence, death so seldom results from this cause, and as without exception probably every anæsthetic is capable of causing such an effect, it is obviously one of the dangers we must anticipate in the use of these compounds, but which we cannot guard against or expunge in our choice of preparations.

Therefore, the dangerous properties of anæsthetics, *i. e.*, those properties which we can avoid in our selection of a compound, resolve themselves, practically into decided depressant effects on the heart and on their containing toxic elements in their composition which may further, and possibly more powerfully, deleteriously affect the system by becoming liberated; and just such properties we find possessed by the group of preparations under consideration. It is taken for granted, of course, that compounds having such dangerous properties as some possess by causing an intense degree of irritation in the lungs and air-passages, etc., would undoubtedly

be avoided if for no other reason than the impracticability of administering them.

It may be said, however, that beneath the truth the writer is burying the truth, in so far that many other anæsthetics have been used not belonging to the above group, of which nothing has been said, and which also act as cardiac depressants, hence, that it must follow that this property of depressing the heart is not one peculiar to any class of anæsthetics, but a very general one. Admitting that other anæsthetics may induce cardiac paralysis before asphyxia is produced,—and it must be acknowledged that certain of them have a special tendency in this direction, such as hydrocyanic acid and creasote, the same as certain of the chlorinated compounds, such as the ethylidene and ethylene chlorides show a more decided tendency to the respiratory centres, but which is readily explained when we consider that the heart is so depressed as to be ineffectual in supplying the respiratory centres with blood,—yet the rule appears to hold good, and, to facilitate a comparison of these two classes of compounds, they are here placed in parallel columns :—

| *Chlorinated, Brominated, and Iodated Anœsthetics.* | *Miscellaneous Anœsthetics.* |
|---|---|
| Chloroform, $CHCl_3$. | Aldehyde, $C_2H_4O$. |
| Chloral hydrate, $C_2HCl_3OH_2O$. | Benzole, $C_6H_6$. |
| Carbon dichloride, $C_2H_4$. | Coal gas. |
| Carbon tetrachloride (chlorocarbon) $CCl_4$. | Creasote, $C_6H_6O$. |
| Bromoform, $CHBr$. | Carbonous oxide, $CO$. |
| Ethyl chloride (chloric ether), $C_2H_5Cl$. | Carbon bisulphide, $CS_2$. |
| Ethyl iodide, $C_2H_5I$. | Ethyl oxide (ether), $C_4H_{10}O$, or $(C_2H_5)_2O$. |
| Ethyl bromide, $C_2H_5Br$. | Ethyl, acetate, $C_2H_3O_2C_2H_5$. |
| Ethylene bichloride (Dutch liquid), $C_2H_4Cl_2$. | Ethyl, methylate, $C_2H_6O\ (CH_3)_2O$. |
| Ethylidene bichloride (ethydene chloride), $C_2H_4Cl_2$. | Ethyl, nitrate, $C_2H_5ONO$. |
| Iodoform, $CHI_3$. | Ethyl, formate, $CHO_2C_2H_5$. |
| Ethylene bromide, $C_2H_4Br_2$. | Acid, hydrocyanic, $C_2N_2H$. |
| Methylene bichloride, $CH_2Cl_2$. | Hydrogen sulphide, $SH_2$. |
| Butyl chloride, $C_4H_9Cl$. | Naphtha. |
| Methyl chloride, $CH_3Cl$. | Nitrous oxide gas, $N_2O_2$. |
| Isobutyl chloride, $C_5H_9Cl$. | Olefiant gas, $C_2H_4$. |
| Methyl iodide, $CH_3I$. | Essential oils, $C_{10}H_{16}$. |
| Amyl iodide, $C_{10}H_{10}I$. | Pyrrol, $C_4H_5N$. |
| Amyl chloride, $C_{10}H_{10}Cl$. | Acetone, $C_3H_6O$. |
| | Amylene, $C_5H_{10}$. |

While these two classes represent the halogen and miscellaneous compounds respectively, yet were two other classes formed from them as representing syncopal and asphyxiating anæsthetics, or those having a decided tendency to depress the heart and those whose tendencies are to compromise the respiratory function, scarcely much change would be made, and with but few exceptions the above division would stand as it is. And while it is to be seriously regretted that our knowledge of the physiological actions of these compounds is so grievously inadequate, and that of

such a small percentage of the whole number we have scarcely sufficient information to be able to assert positively what their action is, yet we do know that every one of the halogen anæsthetics which have been investigated in reference to their action on the arterial pressure and as to their mode of producing death, have been found to both diminish the blood-pressure and paralyze the heart; and that probably at least sixty per cent. of the deaths from chloroform have been due to arrest of the heart; while in regard to the miscellaneous anæsthetics, it is undoubted that some of them do diminish the arterial tension and depress the heart, and will cause death by cardiac paralysis; yet, there seems to exist that unmistakable predominant tendency to produce death by asphyxia and not by sudden cardiac arrest, although with those which possess to any marked degree a cardiac depressant action, a sudden failure of the heart is likely to occur, as with the halogenated compounds. Every anæsthetic has a decided tendency to cause death by asphyxia, and the reason of this is very apparent when we consider how greatly all the functions of animal life are diminished, but particularly those of the nervous system, whose excito-motor functions especially must always be very decidedly lessened in anæsthesia; and when we have such a serious interference with the transmission, reception, and origination of impulses, as is invariably present in complete narcosis, it is not difficult to understand how it is that any anæsthetic possessing this powerful depressant power may, if given in excessive doses (a too concentrated condition of the vapour inhaled), or in states of the system when these centres are in an abnormally impressionable condition, cause a sudden paralysis, such as has followed the use of ether, which, as is generally admitted, is beyond doubt, with but one exception, the safest of all anæsthetics in general use, and the least liable to cause death without a warning such as the merest novice must appreciate. Yet because it must follow that every anæsthetic may and will cause death by asphyxia, the same universal rule does not apply to them in regard to their effects on the circulatory system, and instead of its being the rule to decidedly depress the heart and blood-pressure, excluding the chlorinated, brominated, and iodated compounds, it is probably the exception; therefore, it must be evident that while in the anæsthetic compounds such as creasote and hydrocyanic acid, their decided depressant action on the heart is an accidental concomitant associated with their other physiological properties, on the other hand, in the halogen preparations the action appears to be so universally existent as to suggest that there must be some inherent toxic principle or principles which enter into the composition of each, and is common to all of them, and which endows them with this one dangererous property.

That this toxic principle is not to be found in the radicles forming the bases of these compounds, but in the negative elements, is obvious for several reasons, and some years ago Richardson reached a similar con-

clusion regarding one of these particular divisions, and stated that he deemed all *chlorinated* compounds dangerous. More recently, Squibb has warned us to be careful in the use of ethyl bromide, for fear of inducing brominism; and we know that by giving the ethyl iodide by inhalation, the system is rapidly brought under the influence of iodine. Now, for instance, let us take ether, an oxide of ethyl, and substitute for the oxygen bromine, and what is the result? The ether, which was before a cardiac stimulant, and would almost without exception cause death by asphyxia, has now become excessively increased in power, and the half drachm of the compound will produce an effect more intense than ten or twenty or more times the original amount, and, instead of a cardiac stimulant, we have a decided depressant, and instead of having deaths following from slowly induced asphyxia, we have deaths occurring from cardiac arrest, and sudden, overwhelming, and unanticipated results following its use. Further, take olefiant gas, and we find that when inhaled it possesses but feeble anæsthetic powers and causes death by asphyxia; but add bromine or chlorine to it, and we have powerful anæsthetics and undoubted cardiac depressants.

Considering all these things, there can be but little doubt that the dangerous properties, if not the degrees of potency, of anæsthetics, are decidedly enhanced by the addition of either of the halogens, and it is not at all improbable that these ethers are mostly loosely molecular compounds, some of which are more readily decomposed in the system than others, and that their degree of dangerousness, *cæteris paribus*, depends upon the relative amount and relative physiological power of either of these halogen principles which enter into the composition of any one of them, and upon the degree of fixity of the molecules.